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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,853	11/07/2000	Fulvio Mavilio	1303-110	5693

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,853	MAVILIO, FULVIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/9/04 has been entered. As requested, the amendment under 1.116 received on 5/14/04, has been entered. Claims 1-10, 12, and 17-22 are canceled. Claims 11 and 13-16 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 102

As noted in the advisory action mailed on 8/26/04, the rejection of claims 11 and 13-22 under 35 U.S.C. 102(a) as being anticipated by Lattanzi et al. (May, 1998) J. Clin .Invest., Vol. 101 (10), 2119-2128, is withdrawn in view of applicant's cancellation of claims 17-22 and in view of applicant's submission of the copy of the international search report which shows that the Lattanzi et al. reference was published on May 15, 1998, several days after the filing date of the Italian priority document.

Claim Rejections - 35 USC § 103

The rejection of claims 17-22 under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217 is withdrawn in view of applicant's cancellation of the claims.

The rejection of claims 11, and 13-16 under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant has amended the claims to recite methods of ex vivo gene therapy comprising genetically modifying dermal fibroblasts by a method of myogenic conversion comprising ex-vivo transduction of dermal fibroblasts with a therapeutic gene, and transient transfection of the dermal fibroblasts with a vector encoding a muscle lineage commitment gene under control of a strong promoter, followed by administration of the genetically modified dermal fibroblasts to muscle tissue of a person to receive said therapy, wherein the vector is an adenoviral vector, wherein the muscle lineage commitment gene is myoD, and wherein the rate of myogenic conversion is greater than 40%.

For clarity of prosecution, the rejection of record as it applies to the amended claims is set forth below.

Watt et al. teaches the treatment of muscular disorders such as muscular dystrophy by administering patient derived dermal fibroblasts which have been genetically modified to express a therapeutic gene into muscle tissue (Watt et al., pages 5-7). Specifically, Watt et al. teaches the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy (Watts et al., page 6, and pages 23-24, claims 1-24). Watt et al. does not specifically teach the further modification of these cells with a viral vector encoding myoD. Choi et al. supplements Watt et al. by teaching that primary fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989).

Both Watt et al. and Choi et al. provide the motivation for further transforming fibroblasts which encode dystrophin with a second viral vector encoding myoD. Watt et al. teaches that the preferable method of treatment of muscular dystrophy would modify the patient's own myoblasts to express dystrophin (Watt et al., pages 2-3, bridging paragraph). However, because the use of myoblasts from patients with muscular dystrophy for gene therapy of MD pose several problems because the disease myoblasts have already passed through several bouts of degeneration/regeneration, Watt proposes using transduced fibroblasts since donor fibroblasts can fuse in vivo to make a multinucleate cell which can behave like a muscle cell (Watt et al., page 3, lines 15-22). Choi et al. supplements Watt et al. by teaching that fibroblasts

can be converted to myoblasts by expression of myoD. Thus, based on the motivation for utilizing cells that are capable of behaving like myoblasts for the therapy of MD taught by Watt et al., and the teachings of Choi et al. that transduction of dermal fibroblasts with the myoD gene results in the differentiation of the fibroblasts to actual myoblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to co-express the myoD gene in the fibroblasts taught by Watt et al. in order to differentiate the dystrophin expressing fibroblasts into dystrophin expressing myoblasts for the treatment of muscular disorders such as muscular dystrophy. Further, based on the successful transduction of primary fibroblasts with viral vectors encoding dystrophin and myoD as taught by Watt et al. and Choi et al., the skilled artisan would have had a reasonable expectation of success in preparing a modified fibroblast which has been co-transduced with both the genes for dystrophin and myoD.

The teachings of Watt et al. in view of Choi et al. differ from the instant invention in that Choi et al. does not teach the use of an adenovirus to express myoD in the dermal fibroblasts. Murry et al. supplements Choi et al. by teaching the use of an adenovirus encoding myoD to infect cardiac fibroblasts *in vitro* and *in vivo* resulting in myoconversion (Murry et al., pages 2211-2212). Murry et al. further provides motivation for using the adenovirus encoding myoD over the retrovirus encoding myoD taught by Choi et al. by teaching that fibroblasts infected with adenovirus encoding myoD demonstrated up to 14% myoconversion compared to 5% or less observed with the retrovirus taught by Choi et al. Thus, based on the increased level of myoconversion using adenovirus encoding myoD over retrovirus encoding myoD, as demonstrated by Murry et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use an adenovirus encoding myoD to infect fibroblasts over the retrovirus taught

by Choi et al.. Salvatori et al. further provides motivation for infecting dermal fibroblasts with adenovirus encoding myoD over cardiac fibroblasts in methods of myoconversion by teaching that dermal fibroblasts have a substantially greater capacity to myoconvert than cardiac fibroblasts (Salvatori et al., page 2736, column 1, paragraph 1, and Table I on page 2738). In Table I, Salvatori shows that dermal fibroblasts show 8X the rate of myoconversion as cardiac fibroblasts. and to use those dermal fibroblasts in the methods of *ex vivo* gene therapy taught by Watt et al. Therefore, based on the increased level of myconversion of fibroblasts achieved using adenovirus encoding MyoD over retrovirus encoding MyoD, and the naturally greater capacity of dermal fibroblasts to myoconvert as compared to cardiac fibroblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the adenovirus encoding myoD for the retrovirus encoding myoD in the method of myoconversion of dermal fibroblasts taught by Choi et al. and Watt et al. Further, based on the successful use of the adenovirus encoding myoD to infect and myoconvert cardiac fibroblasts at a rate of 14% and the teachings of Salvatori et al that dermal fibroblasts are 8X better at myoconversion than cardiac myoblasts, the skilled artisan would have had a reasonable expectation of success in using the adenovirus encoding myoD to infect and myoconvert dermal fibroblasts at a rate of 40% or more.

The applicant argues that the amendments to the claims overcomes the rejection of record because the art individually or in combination does not teach or suggest methods of therapy. In response, Watt et al., the primary reference, clearly teaches methods of ex vivo gene therapy for muscular disorders. Specifically, Watt et al. teaches the treatment of muscular disorders such as muscular dystrophy by administering patient derived dermal fibroblasts which have been

genetically modified to express dystrophin into muscle tissue (Watt et al., pages 5-7). Thus, contrary to applicant's assertion, Watt et al. provides the teachings for *ex vivo* gene therapy of muscular disorders.

The applicant further argues that Choi et al. teaches additional culture steps of the transduced cells which are not necessary for applicant's methods and which would result in reduced cell viability and increased cell aging. In response, it is noted that the claims as amended do not place any limitation on the culture conditions during or after the transduction/infection of the dermal fibroblasts. In addition, the claims read broadly on any therapeutic effect derived from the transplanted cells, no matter how transient. Further, the previous office action cited Choi et al. to supplement the teachings of Watt et al. by teaching that primary fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989). While it is true that Choi et al. teaches the culture of the modified fibroblasts for several days, the purpose of the Choi et al. study was to observe the effects of myoD on fibroblast differentiation into myoblasts, a process which takes place over several days, and to study the temporal sequence of gene expression associated with myoconversion. However, Murry et al. et al. makes clear that the process of myoconversion of fibroblasts expressing myoD can occur *in vivo* as well as in tissue culture. Thus, in view of the teachings of Watt et al. to administer genetically modified fibroblasts into muscle, not myoblasts derived from fibroblasts, and the teachings of Murry et al. that fibroblast myoconversion can take place *in vivo* following the expression of myoD, the skilled artisan would have been motivated to transplant the dermal fibroblasts transduced with

adenovirus encoding myoD as taught by Murry et al. prior to their myoconversion in tissue culture.

The applicant also argues that the instant methods are safer than those taught in the art because of the use of non-integrating viral vectors and because no cell-mediated immune responses have been observed at the site of infection using applicant's methods. In response, the rejection of record provides motivation and a reasonable expectation for success in expressing myoD in dermal fibroblasts using a recombinant adenoviral vector which is a non-integrating viral vector. Further, Watt et al. teaches that the use of donor cells derived from the patient to be treated prevents their rejection as foreign. Therefore, applicant's arguments are not found persuasive.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER